

A 5-Year Study of Patients with Pulmonary Tuberculosis in a Concurrent Comparison of Home and Sanatorium Treatment for One Year with Isoniazid plus PAS*

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This report from the Tuberculosis Chemotherapy Centre, Madras, summarizes the progress over a 5-year period of 193 patients with newly diagnosed, sputum-positive pulmonary tuberculosis who were admitted to a concurrent comparison of home and sanatorium treatment for one year with isoniazid plus PAS. Previous reports have shown that, despite the traditional advantages of sanatorium treatment—rest, adequate diet, nursing and supervised drug-administration—the home patients responded nearly as well as the sanatorium patients in the first year; further, the relapse rates over a 2-year period of follow-up were similar. The findings in the present report are based on a 4-year period of follow-up and extend these conclusions, the relapse rates over the period being 7% for the home patients and 10% for the sanatorium patients.

Patients who failed to respond to treatment in the first year and those who had a bacteriological relapse in the second or subsequent years were usually re-treated with reserve regimens, first with streptomycin plus pyrazinamide and, if this was ineffective, with cycloserine plus ethionamide. Considering the findings over the entire 5-year period, five home patients and three sanatorium patients died from non-tuberculous causes. Of the remainder, 5% of the home patients and 6% of the sanatorium patients died of tuberculosis, 4% in each series had bacteriologically active disease at five years and 90% and 89%, respectively, had bacteriologically quiescent disease at that time. These findings are very encouraging, particularly for developing countries such as India, where tuberculosis is a major problem and sanatorium beds are very few.

An earlier publication from the Tuberculosis Chemotherapy Centre, Madras (1959), reported on the findings of a controlled comparison of home and sanatorium treatment of pulmonary tuberculosis, in which all patients received isoniazid plus *p*-aminosalicylic acid (PAS) for one year. The

results in the two series were similar in the first year. Subsequently, all patients were followed up at home and the present report deals with the progress in the second, third, fourth and fifth years of all the patients originally admitted to the comparison and also gives the status of their disease at five years. The relapse rates in the second and third years have already been reported to be similar for the home and sanatorium patients with bacteriologically quiescent disease at one year (Velu et al., 1960a; Devadatta et al., 1961).

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I. PLAN AND CONDUCT OF THE STUDY

CHEMOTHERAPY DURING THE 5-YEAR PERIOD

In the first year, the patients were prescribed isoniazid plus PAS (approximately 4-6 mg/kg body-weight of isoniazid and 0.2-0.3 g/kg of sodium PAS)¹ to be taken in the form of cachets twice a day (Tuberculosis Chemotherapy Centre, Madras, 1959). The treatment policy for the second and third years has been fully described elsewhere (Devadatta et al., 1961). In brief, patients with bacteriologically quiescent disease at one year (see definition overleaf) were allocated at random to treatment for the second year with isoniazid (approximately 4-6 mg/kg body-weight daily, in a single tablet) or to a placebo, calcium gluconate (500 mg daily, in a single tablet). During the third year, half (selected at random) of those who were treated with isoniazid in the second year, and whose disease remained quiescent, continued to receive that drug and all the remaining patients with quiescent disease received the placebo. All patients with quiescent disease at three years received the placebo daily in the fourth year. Those with quiescent disease at four years did not receive any medicament subsequently.

Patients with bacteriologically active disease at one year (see definition overleaf) or those who had a bacteriological relapse were usually treated with streptomycin plus pyrazinamide in the first instance. Patients who failed to respond to this regimen received cycloserine with either ethionamide or thioacetazone.²

In a small proportion (5%) of the patients, the disease was classified at one year as of bacteriologically doubtful status (see definition overleaf). The treatment received by these patients in the second and subsequent years is described on page 542.

INVESTIGATIONS IN THE SECOND, THIRD, FOURTH AND FIFTH YEARS

Patients with bacteriologically quiescent disease at one year were examined clinically and radiographically at monthly intervals in the second year, and at 3-monthly intervals in the third, fourth and

fifth years. The planned intensity of bacteriological examinations is set out in Table 1. The standard procedure was to obtain 14 bacteriological specimens in the second year, 9 in the third, 9 in the fourth and 11 in the fifth year. Occasionally, extra specimens were examined, especially if a positive result had been obtained after a sequence of negative results. Tests of sensitivity to isoniazid and PAS were set up at each of these examinations if a positive culture was obtained. The techniques employed for smear and culture examinations and

TABLE 1
PLANNED INTENSITY OF BACTERIOLOGICAL EXAMINATIONS FOR PATIENTS WITH BACTERIOLOGICALLY QUIESCENT DISEASE AT ONE YEAR

Year	Month	Type and number of specimens	Total number of specimens
Second	13 to 23	One collection specimen ^a or a pair of laryngeal swabs ^a	14
	24	Two collection specimens and a pair of laryngeal swabs	
Third	27, 30 & 33	One collection specimen and a pair of laryngeal swabs	9
	36	Two collection specimens and a pair of laryngeal swabs	
Fourth	39, 42 & 45	One collection specimen and a pair of laryngeal swabs	9
	48	Two collection specimens and a pair of laryngeal swabs	
Fifth	51, 54 & 57	One collection specimen and a pair of laryngeal swabs	11
	59 ½	One collection specimen and one supervised spot specimen	
	60	Two collection specimens and a pair of laryngeal swabs	
Total specimens during the 4-year period of follow-up			43

¹ For instance, a patient weighing 100 lb (45 kg) received 200 mg of isoniazid and 10 g of sodium PAS.

² Thioacetazone is the recommended international non-proprietary name (see World Health Organization, 1962) for 4'-formylacetanilide thiosemicarbazone (thiacetazone, Tb 1-698).

^a For the method of obtaining the specimen, see Velu, Narayana & Subbaiah (1961).

sensitivity tests have been described in detail earlier, as also the details of the grading of smear and culture results and the definition of isoniazid resistance (Tuberculosis Chemotherapy Centre, Madras, 1959).

Patients with active or relapsed disease were examined monthly throughout the period they were receiving chemotherapy. The monthly examinations included a chest radiograph, examination by smear and culture of two collection specimens of sputum, and examination by culture of a pair of laryngeal swabs. Tests of sensitivity to the drugs the patient was receiving were set up on one positive culture at each of these examinations, using techniques described previously (Tuberculosis Chemotherapy Centre, Madras, 1959; Angel et al., 1963).

COLLAPSE THERAPY AND RESECTION

The policy was not to use collapse therapy or resection. In the event, two patients had surgical treatment—one a pneumonectomy (see page 545) and the other a decortication for a pyopneumothorax with a bronchopleural fistula (see page 543).

DEFINITIONS USED IN THIS REPORT

At one year

Bacteriologically quiescent disease: that is, all cultures (usually 7-9) negative at 10, 11 and 12 months.

Disease of bacteriologically doubtful status: that is, a single positive culture at 10, 11 or 12 months,

following culture negativity at three or more consecutive monthly examinations.

Bacteriologically active disease: that is, either

- (a) serious radiographic deterioration with one or more positive cultures necessitating a change of chemotherapy during the first year; or
- (b) cultures never all negative at three consecutive monthly examinations; or
- (c) a total of two or more positive cultures at 10, 11 and 12 months following culture negativity at three or more consecutive monthly examinations.

During the second, third, fourth and fifth years

Bacteriological relapse: that is, two or more positive cultures in any 6-month period. In the second year, this meant a total of two or more positive cultures in seven consecutive monthly examinations. In the subsequent years, when examinations were performed every three months, this meant a total of two or more positive cultures in three consecutive 3-monthly examinations—for example, at 30, 33 and 36 months.

At five years

Bacteriologically quiescent disease:¹ that is, all cultures (usually 9) negative from 54 to 60 months, inclusive.

Bacteriologically active disease: that is, a total of two or more positive cultures from 54 to 60 months, inclusive.

II. CLASSIFICATION OF PATIENTS

Of 193 patients who were admitted to the study (Table 2), 96 were allocated to treatment at home (home series) and 97 to treatment in sanatorium (sanatorium series). The main analysis of the findings in the first year (Tuberculosis Chemotherapy Centre, Madras, 1959) concerned 163 patients (82 home, 81 sanatorium) who (a) had organisms sensitive to isoniazid and PAS on admission, (b) had had no previous chemotherapy (two had received up to two weeks' chemotherapy) and (c) had followed the allocated treatment regimen for 12 months, apart from minor variations, unless they died or had a change of chemotherapy because of deterioration; of these, 130 had bacteriologically quiescent

disease at one year, 10 had disease of bacteriologically doubtful status, 19 had active disease and four had died (three of tuberculosis and the fourth from electrocution). The remaining 30 patients (14 home, 16 sanatorium) were excluded from the main analysis for reasons given in Table 2.

PLAN OF THE PRESENT REPORT

The progress in the second, third, fourth and fifth years is described for patients with bacteriologically

¹ Seven patients, who each produced one positive culture between 54 and 60 months, are also included in this category. In all seven, the culture was an isolated positive (see definition on page 540).

TABLE 2
CLASSIFICATION OF PATIENTS IN THE PRESENT REPORT

		Home	Sana- torium	Both series	Section of report in which progress is considered
Patients included in the main analysis ^a in the first year, according to the classification of their disease status at one year ^b	(a) Bacteriologically quiescent disease	60	70	130	III
	(b) Disease of bacteriologically doubtful status	7	3	10	IV
	(c) Bacteriologically active disease	13	6	19	V
	(d) Death	2	2	4	—
	Total	82	81	163	
Patients excluded from the main analysis in the first year	(a) Isoniazid-resistant organisms on admission	6	3	9	VI
	(b) PAS-resistant organisms on admission	4	2	6	
	(c) Previous chemotherapy of more than two weeks' duration, but with organisms sensitive to isoniazid and PAS	2	2	4	
	(d) Prolonged desensitization to PAS	0	1	1	
	(e) Premature discharge from treatment	0	7	7	
	(f) Sanatorium stay of more than six weeks (home patients)	1	—	1	
	(g) Non-tuberculous death from diseases which influenced the course of the tuberculosis	1	1	2	
	Total	14	16	30	
All patients admitted to the study		96	97	193	VII

^a For definition, see preceding page.

^b For details of classification, see preceding page.

quiescent disease at one year in section III, for those with disease of bacteriologically doubtful status at one year in section IV, for patients with active disease at one year in section V and for patients not

included in the main analysis in section VI. Section VII summarizes the disease status at five years of all the 193 patients admitted to the study. (See also Table 2.)

III. THE PROGRESS OF PATIENTS WITH BACTERIOLOGICALLY QUIESCENT DISEASE AT ONE YEAR DURING A 4-YEAR PERIOD OF FOLLOW-UP

Of the 130 patients with bacteriologically quiescent disease, four were not allocated at random to treatment in the second year for reasons given by Velu et al. (1960a). Their progress is reported on page 542.

Of the remaining 126, 57 had been treated at home in the first year (home series) and 69 in sanatorium (sanatorium series); 65 were allocated to isoniazid alone (isoniazid series) and 61 to calcium gluconate (calcium series). On the basis of a postero-anterior

radiograph and tomograms, 42 of these were classified by an independent assessor (Dr J. H. Angel) as having residual cavitation at one year (cavitated series) and 84 as having no residual cavitation (non-cavitated series). Their progress is now considered.

DEATHS

Three patients died during the 4-year period of follow-up, all from non-tuberculous causes. One

(home, cavitated, isoniazid) died suddenly in the 17th month, possibly due to a spontaneous pneumothorax, another (home, non-cavitated, calcium) died in the 41st month from carcinoma of the bronchus, and the third (sanatorium, cavitated, calcium) died in the 51st month from cirrhosis of the liver. These patients had only negative cultures for 14, 39 and 49 months, respectively, before death (apart from the first, who had one positive culture two months before death).

BACTERIOLOGICAL RELAPSE IN THE 4-YEAR PERIOD OF FOLLOW-UP

During the 4-year period of follow-up, 11 (8.7%) patients had a bacteriological relapse, eight (6.3%) in the second year (that is, in the first year of follow-up), one (0.8%) in the third, none in the fourth and two (1.6%) in the fifth year. Thus, most of the relapses occurred in the second year.

Table 3 presents the relapse rates for the 126 patients referred to above, according to:

- (a) the place of treatment in the first year (home or sanatorium);
- (b) the cavitation status at the end of the first year (cavitated or non-cavitated);
- (c) the treatment received in the second year (calcium or isoniazid).

The two series in each of the above three contrasts were compared for the condition of disease at the

end of the first year, that is, at the starting-point of the study of relapse. The detailed findings have been reported earlier by Velu et al. (1960a), who concluded that patients in the home series had rather more extensive residual radiographic lesions than those in the sanatorium series as did the cavitated compared with the non-cavitated series, while the calcium and the isoniazid series were fairly similar, both clinically and radiographically, at the end of the first year.

The proportion of patients who had a bacteriological relapse during the 4-year period of follow-up was 7% of 57 home patients, as compared with 10% of 69 sanatorium patients; 10% of 42 patients with cavitation at one year, as compared with 8% of 84 with non-cavitated disease at one year; and 13% of 61 who received calcium gluconate, as compared with 5% of 65 who received isoniazid alone. (The intensity with which patients were examined bacteriologically during the 4-year period of follow-up was similar for the two series in each of the three contrasts above.) None of the differences is statistically significant.

In Table 4, the 126 patients with quiescent disease at one year are classified into 8 subgroups according to the place of treatment in the first year, the cavitation status at the end of the first year and the treatment during the second year; further, the numbers of relapses are set out year by year. It will be observed that, in patients with no residual cavitation at one year, seven of 42 who received

TABLE 3
RELAPSE RATES DURING THE 4-YEAR PERIOD OF FOLLOW-UP
FOR THE THREE CONTRASTS

Contrast		Total patients	Patients who had a bacteriological relapse during the 4-year period of follow-up	
			No.	%
Place of treatment in the first year	Home	57	4	7
	Sanatorium	69	7	10
Cavitation status at one year	Cavitated	42	4	10
	Non-cavitated	84	7	8
Treatment during the second year	Calcium	61	8	13
	Isoniazid	65	3	5
Total		126	11	8.7

TABLE 4
PATIENTS IN THE EIGHT SUBGROUPS WHO HAD A BACTERIOLOGICAL RELAPSE
DURING THE 4-YEAR PERIOD OF FOLLOW-UP

Place of treatment during the first year	Cavitation status at one year	Treatment during the second year	Total patients	Patients who had a bacteriological relapse					
				No.	%	Year of relapse			
						Second	Third	Fourth	Fifth
Home	Cavitated	Calcium	11	1	(9) ^a	1	0	0	0
		Isoniazid	10	0	(0)	0	0	0	0
	Non-cavitated	Calcium	18	3	(17)	1	1	0	1
		Isoniazid	18	0	(0)	0	0	0	0
Sanatorium	Cavitated	Calcium	8	0	(0)	0	0	0	0
		Isoniazid	13	3	(23)	3	0	0	0
	Non-cavitated	Calcium	24	4	(17)	3	0	0	1
		Isoniazid	24	0	(0)	0	0	0	0
All patients			126	11	8.7	8	1	0	2

^a The parentheses indicate percentages based on fewer than 25 observations.

calcium gluconate in the second year had a relapse, as compared with none of 42 who received isoniazid, statistically a highly significant difference ($P < 0.02$). The findings were, however, different in patients with residual cavitation at one year. Thus, one of 19 patients who received calcium gluconate had a relapse, as compared with three of 23 who received isoniazid. In conclusion, whereas isoniazid given alone in the second year prevented relapse among the patients with non-cavitated disease at one year, it apparently conferred no benefit on the patients with cavitated disease at one year.

ISONIAZID ALONE IN THE THIRD YEAR IN THE PREVENTION OF BACTERIOLOGICAL RELAPSE

Sixty patients, who had received isoniazid alone in the second year and had bacteriologically quiescent disease at two years, were allocated at random to treatment in the third year, 30 to isoniazid alone and 30 to calcium gluconate.

An analysis of the clinical and radiographic condition of the two groups at the time of original admission to treatment, at the end of one year and at the end of two years showed no important differences between them (Devadatta et al., 1961). Also, the intensity of bacteriological investigation during the third, fourth and fifth years was similar. During

this period, there were no relapses in either the isoniazid or the calcium group, which suggests that the administration of isoniazid alone in the third year did not apparently confer any benefit.

DETAILS OF THE PATIENTS WHO HAD A BACTERIOLOGICAL RELAPSE

Table 5 gives the details of the 11 patients who had a bacteriological relapse. Clear-cut radiographic deterioration, confirmed by an independent assessor (Dr K. S. Sanjivi), followed the bacteriological relapse in 10 of these patients (including P154 in whom it occurred at 62 months). The 11th patient (P181) produced positive cultures repeatedly.

At the time of relapse, six of the eight patients who received calcium excreted isoniazid-sensitive organisms, as compared with one of the three who were receiving isoniazid, and even in the case of this patient, who was very irregular in taking isoniazid, the next positive culture was isoniazid-resistant. (All 11 patients had only isoniazid-sensitive cultures during the first year of treatment.)

Nine of the 11 patients were treated with streptomycin plus pyrazinamide. Four patients responded favourably and had quiescent disease at five years. Three patients (including one who refused streptomycin injections) failed to respond to this regimen

TABLE 5
DETAILS OF THE PATIENTS WHO HAD A BACTERIOLOGICAL RELAPSE, THEIR SUBSEQUENT CHEMOTHERAPY AND DISEASE STATUS
AT FIVE YEARS

Serial number	Place of treatment during the first year	Cavitation status at one year	Treatment during the second year	Months at which one or more positive cultures were isolated ^a	Results of isoniazid-sensitivity tests ^b	Month retreatment started	Chemotherapy ^c	Disease status at five years ^d
P163	Home	Cavitated	Calcium	22, 23, 24 (2)	S, S, U	24	SZ (18) ^e	Quiescent
P181	Sanatorium	Cavitated	Isoniazid	13, 15, 17, 18, 20, 21, 23, 24 (2), 25	All R	26	SZ (6)	Quiescent
P159	Sanatorium	Cavitated	Isoniazid	15 (3)	R	17	SZ (25)	Quiescent
P90	Sanatorium	Cavitated	Isoniazid	18 (3), 22 (2), 23 (3)	S, R, S	24	SZ (2); PH (4); CEP (3)	Tuberculous death
P132	Sanatorium	Non-cavitated	Calcium	14, 15, 16, 25, 28 (6)	C, R, R, S, R	29	SZ (18)	Quiescent
P191	Sanatorium	Non-cavitated	Calcium	14, 15 (3), 16 (2)	All S	17	SZ (8); PH (24)	Quiescent
P182	Home	Non-cavitated	Calcium	16, 21, 24, 28, 30, 53, 54 (5)	S, S, U, S, S, S, S	54	SZ (6)	Active
P60	Sanatorium	Non-cavitated	Calcium	17, 18, 19, 20, 21, 22	S, S, U, S, S, U	22	SZ (9); PH (17)	Quiescent
P34	Home	Non-cavitated	Calcium	27 (2), 42, 45, 51, 54 (4)	All R	54	SZ (6)	Active
P19	Sanatorium	Non-cavitated	Calcium	43, 54 (3), 55 (4), 56 (2)	All S	56	PH (4)	Active
P154	Home	Non-cavitated	Calcium	57, 60	Both S	—	Nil	Active

^a When more than one positive culture was obtained in a month, the number is indicated in parentheses.

^b S = sensitive; R = resistant; C = contaminated; U = untested.

^c H = isoniazid; P = PAS; S = streptomycin; Z = pyrazinamide; C = cycloserine; E = ethionamide.

^d For details of classification, see page 535.

^e The figures in parentheses give the duration in months.

and, because they had had a relapse with organisms sensitive to isoniazid, were re-treated with isoniazid plus PAS; two achieved quiescent disease at five years and the third died of tuberculosis at 39 months despite a further change of regimen to ethionamide, cycloserine and PAS. At five years, the remaining two patients had not completed 12 months of treatment with streptomycin plus pyrazinamide; one had had positive cultures throughout the six months of treatment and the other, although having active disease by definition, had had only negative cultures at the last three monthly examinations. The 10th patient, who had a relapse at 54 months with isoniazid-sensitive organisms, had, at five years, been treated with isoniazid plus PAS for four months and had had negative cultures at the last three monthly examinations. The 11th patient, who had a positive culture at 57 months, did not have treatment restarted before the end of five years because the second positive culture was only obtained at 60 months. In summary, of the 11 patients who had a bacteriological relapse, six had bacteriologically quiescent disease at five years, four had active disease and one died of tuberculosis.

PROGNOSTIC IMPORTANCE OF VARIOUS FACTORS IN THE OCCURRENCE OF RELAPSE

The prognostic importance of various factors in the occurrence of relapse in the 4-year period have been investigated. The erythrocyte sedimentation rate (ESR), extent of cavitation and grade of smear positivity of the sputum on admission were not of prognostic importance, nor were the month of sputum conversion in the first year and the ESR at one year. However, of 29 patients who had unilateral disease on admission to treatment and bacteriologically quiescent disease at one year, none had a relapse during the 4-year period of follow-up, as compared with 11 of 97 patients who had bilateral disease on admission; this difference does not, however, attain statistical significance ($P=0.1$). Similarly, none of 32 patients who had unilateral disease at one year had a relapse subsequently, as compared with 11 of 90 patients who had bilateral disease ($P=0.06$).

PATIENTS WITH ISOLATED POSITIVE CULTURES

In this report, an isolated positive culture is defined as one positive culture in any 6-month period during the second or subsequent years. A total of 18 (14%) patients had an isolated positive culture

(Table 6), five of them in the second, one in the third, seven in the fourth and five in the fifth year. Eleven of the isolated positive cultures were obtained from sputum specimens and all were negative on direct smear examination; the remaining seven specimens were from laryngeal swabs. A single colony grew in seven of the cultures and only four cultures grew more than 100 colonies (2+ or 3+ growth). The organisms were sensitive to isoniazid in 10 of the 15 cultures with test results available (including three from patients who were receiving isoniazid when the culture was produced).

An isolated positive culture was produced by seven (11%) of 61 patients who received the placebo in the second year, as compared with 11 (17%) of 65 patients who received isoniazid in the second year ($P=0.5$). Of 84 patients with non-cavitated disease, 12 (14%) had an isolated positive culture, as compared with six (14%) of 42 patients with cavitated disease. Thus, the occurrence of the isolated positive result (sometimes even in the fifth year) was apparently not influenced either by the cavitation status at one year, or by whether or not the patient had received isoniazid subsequently.

The occurrence of an isolated positive culture result did not carry a bad prognosis. Thus, only one (6%) of 18 patients with an isolated positive culture had a relapse and one died of a non-tuberculous cause; the remaining 16 patients had bacteriologically quiescent disease at five years and have been regarded as having had bacteriologically quiescent disease throughout the period of follow-up.

OTHER ASSESSMENTS OF PROGRESS

This subsection presents the findings of the radiographic assessments and ESR determinations for the 112 patients who had bacteriologically quiescent disease throughout the period of follow-up; of the remaining 14 patients, 11 had a bacteriological relapse and three died of non-tuberculous causes; eight of the relapses and one of the deaths occurred in the second year. All the radiographic assessments were undertaken by an independent assessor (Dr Raj Narain).

Changes in radiographic appearances

In 58 (52%) of the 112 patients, changes in radiographic appearances had occurred between one and five years. There was improvement in 33 (29%), which was classified as moderate in 2 and slight in 31, and deterioration in 25 (22%), which was classified as moderate in 3 and slight in 22.

TABLE 6
PATIENTS WHO PRODUCED AN ISOLATED POSITIVE CULTURE DURING THE 4-YEAR PERIOD OF FOLLOW-UP

Serial number	Place of treatment in the first year	Cavitation status at one year	Treatment during the second year	Treatment during the third year	Month of positive culture	Bacteriological results		Result of isoniazid-sensitivity test ^b
						Smear ^a	Culture	
P66	Home	Cavitated	Calcium	Calcium	42	—	1+	R
P185	Sanatorium	Cavitated	Calcium	Calcium	42	—	1 colony	R
P152	Home	Cavitated	Calcium	Calcium	45	—	1 colony	S
P30 ^c	Home	Cavitated	Isoniazid	—	15	0	1+	No growth
P59	Home	Cavitated	Isoniazid	Calcium	48	—	1+	S
P77	Home	Cavitated	Isoniazid	Calcium	54	—	1 colony	S
P11	Home	Non-cavitated	Calcium	Calcium	16	0	3+	S
P15	Sanatorium	Non-cavitated	Calcium	Calcium	24	—	1+	R
P19	Sanatorium	Non-cavitated	Calcium	Calcium	43	0	2+	S
P158	Sanatorium	Non-cavitated	Calcium	Calcium	60	0	1 colony	S
P26	Home	Non-cavitated	Isoniazid	Calcium	13	0	4 colonies	S
P6	Sanatorium	Non-cavitated	Isoniazid	Calcium	14	0	1+	S
P139	Sanatorium	Non-cavitated	Isoniazid	Calcium	39	0	1 colony	No growth
P81	Sanatorium	Non-cavitated	Isoniazid	Calcium	54	0	2+	Contaminated
P130	Home	Non-cavitated	Isoniazid	Calcium	60	0	1 colony	R
P114	Sanatorium	Non-cavitated	Isoniazid	Isoniazid	36	—	16 colonies	S
P121	Home	Non-cavitated	Isoniazid	Isoniazid	45	0	1 colony	S
P148	Sanatorium	Non-cavitated	Isoniazid	Isoniazid	59	0	2+	R

^a A dash (—) indicates that the specimen was a laryngeal swab and therefore had no smear result.

^b S = sensitive; R = resistant.

^c This patient died in the 17th month (see page 536).

Radiographic changes, interpreted as deterioration (usually slight), occurred at some time or other during the period of follow-up (four assessments were undertaken) in as many as 35 (31%) of the patients.

Cavitation changes were assessed by using standard radiographs and tomograms. Of 36 patients with cavitation at one year, cavitation had disappeared by five years in 33%, had decreased in 36%, had remained unchanged in 11% and had increased in 19%. Of 76 patients with no cavitation at one year, cavitation was present at five years in five (7%). Thus, increase in or appearance of cavitation occurred in 12 (11%) of the 112 patients with persisting bacteriologically quiescent disease.

Erythrocyte sedimentation rate

The proportion of patients who had an elevated ESR (more than 10 mm) was 75% at one year, 70% at two years, 72% at three years, 65% at four years and 60% at five years. The corresponding proportions were 51%, 35%, 43%, 43% and 34%, respectively, for an ESR of 21 mm or more, and 12%, 7%, 11%, 13% and 11%, respectively, for an ESR of 51 mm or more.

In summary, minor radiographic changes (interpreted as deterioration), minor changes in cavitation and elevated ESRs occurred not infrequently in patients with persisting bacteriologically quiescent disease.

PATIENTS NOT ALLOCATED AT RANDOM

Of the four patients not included in the random allocation to treatment (see page 536), one (home, cavitated) died of carcinoma of the oesophagus in the 15th month, having had negative cultures for the preceding 13 months; two others (1 home, 1 sanatorium; both non-cavitated) received no further

chemotherapy and had negative cultures throughout the 4-year period, and the fourth (home, cavitated), who continued on isoniazid plus PAS, had a bacteriological relapse in the 15th month with isoniazid-resistant organisms, was treated with streptomycin plus pyrazinamide for 18 months and had quiescent disease at five years.

IV. PATIENTS WITH DISEASE OF BACTERIOLOGICALLY DOUBTFUL STATUS AT ONE YEAR

Ten patients were classified as having disease of bacteriologically doubtful status at one year (see definition on page 535), the single positive culture occurring in the 10th month in three, in the 11th in two and in the 12th in five patients. In the second year, seven patients received calcium gluconate, two isoniazid, and one continued on isoniazid plus PAS. Five patients had negative cultures throughout the 4-year period of follow-up. Two produced an isolated positive culture at 33 and 54 months, respectively, which was sensitive to isoniazid. In the remaining three patients, the positive culture obtained at 12 months proved to be the beginning of a bacteriological relapse. One of these patients, who received isoniazid in the second and third years,

had four positive cultures in the second year followed by a series of negative cultures and then three more positive results in the third year; she had one more positive result at 39 months, but 22 subsequent cultures were negative and the disease was quiescent at five years. The remaining two patients were treated with streptomycin plus pyrazinamide for 15 and 18 months, and had quiescent disease at five years.

In summary, the three patients who had a bacteriological relapse had positive cultures at 12 and 13 months—that is, the positive culture at 12 months proved to be the commencement of a relapse. Finally, all 10 patients who had disease of bacteriologically doubtful status at one year had bacteriologically quiescent disease at five years.

V. PATIENTS WITH BACTERIOLOGICALLY ACTIVE DISEASE AT ONE YEAR

There were 19 patients with bacteriologically active disease at one year (see definition on page 535); their chemotherapy during the 4-year period of follow-up and their disease status at five years are set out in Table 7. One of the 11 who continued with isoniazid plus PAS in the second year attained and maintained bacteriologically quiescent disease as did two of the three who received isoniazid alone. In all, 16 patients received streptomycin plus pyrazinamide. Of these, seven had bacteriologically quiescent disease at five years, one died from a non-tuberculous cause (bronchial carcinoma), two died of tuberculosis, and six others failed to respond to treatment. Of the six patients who failed to respond to treatment, four were treated with cyclo-

serine plus ethionamide; at five years, three of these had bacteriologically quiescent disease and the fourth, who was still under treatment, had had only negative cultures at the last two monthly examinations. The remaining two patients were treated with cycloserine plus thioacetazone followed by other regimens (see Table 7); one died of tuberculosis and the other had active disease at five years.

In summary, of the 19 patients with bacteriologically active disease at one year, 13 had bacteriologically quiescent disease and two had bacteriologically active disease at 5 years; four had died, three from tuberculosis and one from a non-tuberculous cause.

TABLE 7
CHEMOTHERAPY DURING THE 4-YEAR PERIOD OF FOLLOW-UP AND DISEASE STATUS
AT FIVE YEARS FOR PATIENTS WITH BACTERIOLOGICALLY ACTIVE DISEASE AT ONE YEAR

Serial number	Place of treatment during the first year	Regimens of chemotherapy during the 4-year period of follow-up ^a	Disease status at five years ^b
P67	Home	PH (12) ^c	Quiescent
P43	Home	H (24)	Quiescent
P111	Sanatorium	H (24)	Quiescent
P23	Home	SZ (24)	Quiescent
P69	Home	SZ (23)	Quiescent
P100	Home	SZ (21)	Quiescent
P42	Sanatorium	SZ (12)	Non-tuberculous death
P115	Home	SZ (9)	Tuberculous death
P88	Home	PH (12); SZ (24)	Quiescent
P127	Home	PH (12); SZ (24)	Quiescent
P149	Sanatorium	PH (12); SZ (24)	Quiescent
P179	Home	H (5); SZ (24)	Quiescent
P75	Home	PH (7); SZ (2)	Tuberculous death
P177	Sanatorium	PH (8); SZ (6); CE (18)	Quiescent
P13	Home	PH (12); SZ (9); CE (18)	Quiescent
P38	Home	PH (13); SZ (7); CE (18)	Quiescent
P31	Sanatorium	PH (14); SZ (1); CE (4)	Active
P135	Home	PH (4); SZ (7); CT (3); CE (5); CH (10); H (3); EH (5)	Active
P116	Sanatorium	PH (5); SZ (8); CT (12); H (3); CE (8)	Tuberculous death

^a H = isoniazid; P = PAS; S = streptomycin; Z = pyrazinamide; C = cycloserine; E = ethionamide; T = thioacetazone.

^b For details of classification, see page 535.

^c The figures in parentheses give the duration in months.

VI. PATIENTS NOT INCLUDED IN THE MAIN ANALYSIS

Of the 30 patients excluded from the main analysis, three died during the first year, one from tuberculosis in the first month and two from non-tuberculous causes in the eighth and ninth months, respectively (Tuberculosis Chemotherapy Centre, Madras, 1959). For the remaining 27 patients, the chemotherapy during the 4-year period of follow-up and the disease status at one and at five years are set out in Table 8.

Of the eight patients with isoniazid-resistant organisms on admission, two responded unfavour-

ably to treatment: one died of tuberculosis in the 18th month while receiving streptomycin plus pyrazinamide and the other had bacteriologically active disease at five years in spite of having received five different regimens of chemotherapy; both had had active disease at one year. The remaining six patients, two of whom had had active disease and four quiescent disease at one year, had quiescent disease at five years (including one (P107) who had had a decortication for a pyopneumothorax with a bronchopleural fistula). Four of these (including one of the cases

TABLE 8
CHEMOTHERAPY DURING THE 4-YEAR PERIOD OF FOLLOW-UP AND DISEASE STATUS
AT ONE AND FIVE YEARS FOR PATIENTS EXCLUDED FROM THE MAIN ANALYSIS

Reason for exclusion from main analysis	Serial number	Place of treatment in the first year	Disease status at one year ^a	Regimens of chemotherapy during the 4-year period of follow-up ^b	Disease status at five years ^a
Isoniazid-resistant organisms on admission	P40	Home	Active	SZ (5) ^c	Tuberculous death
	P64	Sanatorium	Active	PH (12); SZ (10); CT (11); CE (7); H (8)	Active
	P33	Home	Active	PH (5); SZ (24)	Quiescent
	P98	Home	Active	—	Quiescent
	P119	Sanatorium	Quiescent	SZ (8); CE (24)	Quiescent
	P107	Home	Quiescent	SPH (2); PH (9)	Quiescent
	P133	Home	Quiescent	H (27)	Quiescent
	P29	Sanatorium	Quiescent	H (12)	Quiescent
Premature discharge from treatment	P108	Sanatorium	Active	—	Tuberculous death
	P126	Sanatorium	Active	CT (8); CE (2); ZE (2)	Tuberculous death
	P76	Sanatorium	Favourable ^d	PH (7)	Active
	P73	Sanatorium	Active	PH (13); H (6)	Quiescent
	P63	Sanatorium	Favourable ^e	Received chemotherapy elsewhere but details not complete	Quiescent
	P93	Sanatorium			Quiescent
	P138	Sanatorium			Quiescent
PAS-resistant organisms on admission	P25	Sanatorium	Active	PH (18); SZ (12)	Quiescent
	P27	Home	Quiescent	H (24)	Quiescent
	P193	Home	Quiescent	H (13)	Quiescent
	P24	Sanatorium	Quiescent	—	Quiescent
	P55	Home	Quiescent	—	Quiescent
	P151	Home	Quiescent	—	Quiescent
Previous chemotherapy of more than two weeks' duration, but with organisms sensitive to isoniazid and PAS	P123	Home	Active	PH (6); SZ (13)	Quiescent
	P22	Sanatorium	Quiescent	PH (24)	Quiescent
	P187	Sanatorium	Quiescent	H (24)	Quiescent
	P188	Home	Quiescent	—	Quiescent
Prolonged desensitization to PAS	P17	Sanatorium	Quiescent	H (12)	Quiescent
Sanatorium stay of more than six weeks (home patients)	P113	Home	Quiescent	H (27)	Quiescent

^a For details of classification, see page 535.

^b H = Isoniazid; P = PAS; S = streptomycin; Z = pyrazinamide; C = cycloserine; E = ethionamide; T = thioacetazone.

^c The figures in parentheses give the duration in months.

^d This patient had four negative cultures at 12 months.

^e These patients had four, one and three negative cultures, respectively, at 12 months.

with active disease at one year) did so without receiving reserve regimens; the fifth, who had had active disease at one year, attained quiescent disease on streptomycin and pyrazinamide; and the sixth, who had a relapse, attained quiescent disease on cycloserine plus ethionamide after failing to respond to streptomycin plus pyrazinamide.

Of the seven patients who discharged themselves from treatment during the first year, three responded unfavourably: two died of tuberculosis (in the 18th and 50th months, respectively), the first having had no further chemotherapy after the first year and the second while receiving his third reserve regimen; the third patient, who was very uncooperative and had only had seven months of treatment with isoniazid plus PAS after the first year, had active disease at five years. The remaining four patients, three of whom had received further chemo-

therapy (two at other tuberculosis clinics) and one, who had apparently received no further treatment, had quiescent disease at five years.

The remaining 12 patients attained quiescent disease at five years (including one (P22) who had had a pneumonectomy), the only two with active disease at one year having subsequently received treatment with a reserve regimen—namely, streptomycin plus pyrazinamide.

In summary, at five years, 22 patients had bacteriologically quiescent disease, two had active disease and six had died, four from tuberculosis and two from non-tuberculous causes. The six patients who were classified at five years as having had an unfavourable response had either had isoniazid-resistant organisms on admission or had discharged themselves from treatment in the first year.

VII. DISEASE STATUS AT FIVE YEARS OF ALL PATIENTS

There were 96 patients who were treated at home and 97 patients who were treated in sanatorium in the first year. During the subsequent four years, 12 of the home patients and 6 of the sanatorium patients had to be hospitalized for tuberculous conditions, a non-significant difference. The period of hospitalization was less than one month in two (1 home, 1 sanatorium), 1-3 months in four (3 home, 1 sanatorium), 3-6 months in four (3 home, 1 sanatorium), 6-12 months in four (3 home, 1 sanatorium) and one year or more in four (2 home, 2 sanatorium).

During the 5-year period, eight patients (5 home, 3 sanatorium) died from non-tuberculous causes: seven had consistently had negative cultures for

2, 4, 13, 14, 18, 39 and 49 months, respectively, before death and the eighth (sanatorium) had positive cultures at the time of death, which was due to carcinoma of the tongue. Of the remaining 91 patients in the home series, 82 (90%) had bacteriologically quiescent disease at five years, as compared with 84 (89%) of the 94 sanatorium patients; five (5%) and six (6%), respectively, had died of tuberculosis and four (4%) in each series had bacteriologically active disease (Table 9). Thus, the condition of the home and sanatorium series was very similar at five years. Considering both series together, 90% of the patients had bacteriologically quiescent disease at five years, 4% had active disease and 6% had died of tuberculosis.

VIII. DISCUSSION

The present report is concerned with the progress during a 5-year period of 193 patients with pulmonary tuberculosis who were admitted to a concurrent comparison of home and sanatorium treatment for one year with isoniazid plus PAS. The patients had newly diagnosed, untreated and usually far-advanced disease on admission to treatment, and came mostly from the poorest sections of the community in Madras city. Unless their condition

necessitated a period of treatment *in hospital* (which was uncommon), during the 4-year follow-up period all the patients lived in their normal home environment—that is, they were housed in poor and overcrowded accommodation, had a low dietary intake and engaged in strenuous physical activity, often working for long hours (Ramakrishnan et al., 1961b, 1966¹).

¹ See article on page 553 of this issue.

TABLE 9
DISEASE STATUS AT FIVE YEARS FOR ALL HOME PATIENTS AND ALL SANATORIUM PATIENTS ADMITTED TO STUDY

Bacteriological classification of disease status at five years ^a										
	Home series					Sanatorium series				
	Total	Quiescent		Active	Tuberculous death	Total	Quiescent		Active	Tuberculous death
		No.	%				No.	%		
<i>Patients included in the main analysis in the first year ^b</i>										
(a) Bacteriologically quiescent disease at one year ^a	57	54	95	3	0	69	67	97	1	1
(b) Disease of bacteriologically doubtful status at one year ^a	7	7	(100) ^c	0	0	3	3	(100)	0	0
(c) Bacteriologically active disease at one year ^a	13	10	(77)	1	2	5	3	(60)	1	1
(d) Tuberculous death in the first year	1	—	—	—	1	2	—	—	—	2
<i>Patients excluded from the main analysis in the first year</i>										
(a) Isoniazid-resistant organisms on admission	6	4	(67)	0	2 ^d	3	2	(67)	1	0
(b) PAS-resistant organisms on admission	4	4	(100)	0	0	2	2	(100)	0	0
(c) Previous chemotherapy of more than two weeks' duration, but with organisms sensitive to isoniazid and PAS	2	2	(100)	0	0	2	2	(100)	0	0
(d) Prolonged desensitization to PAS	0	—	—	—	—	1	1	(100)	0	0
(e) Premature discharge from treatment	0	—	—	—	—	7	4	(57)	1	2
(f) Sanatorium stay of more than six weeks (home patients)	1	1	(100)	0	0	—	—	—	—	—
Total patients	91	82	90	4	5	94	84	89	4	6
Non-tuberculous death during the 5-year period	5	—	—	—	—	3	—	—	—	—
All patients admitted to study	96	—	—	—	—	97	—	—	—	—

^a For details, see page 535.

^b For definition, see page 535.

^c The parentheses indicate percentages based on fewer than 25 observations.

^d Including one in the first year.

RELAPSE RATES IN PATIENTS WITH BACTERIOLOGICALLY QUIESCENT DISEASE AT ONE YEAR

About 90% of the patients with bacteriologically quiescent disease at one year maintained this state throughout the 4-year period of follow-up. There were 11 (8.7%) bacteriological relapses; eight of these occurred in the first year of follow-up, so that the risk of relapse was maximal during this period. The relapse rate was no higher in the home series than in the sanatorium series; thus, four (7%) of 57 home patients had a relapse, as compared with seven (10%) of 69 sanatorium patients.

Isoniazid alone, given in the second year, prevented relapse among the patients with bacteriologically quiescent disease and no residual cavitation at one year; none of 42 such patients had a relapse, as compared with seven (17%) of 42 who received a placebo (calcium gluconate), statistically a highly significant difference ($P < 0.02$). On the other hand, isoniazid alone in the second year apparently had no effect in preventing relapses among the patients with residual cavitation at one year, since three (13%) of 23 cavitated patients who received it had a relapse, as compared with one (5%) of 19 who received the placebo.

A subsidiary study, based on random allocation, showed that, in patients with bacteriologically quiescent disease at two years following a year of isoniazid plus PAS and a year of isoniazid alone, the administration of isoniazid in the third year conferred no apparent benefit, there being no relapses in either the treated or the control group. Although based on small numbers, this finding underlines the importance of control groups in interpreting the results of long-term chemotherapy studies and, in particular, the need for caution in assessing recommendations made by some workers for very prolonged chemotherapy (Doonief, Hite & Bloch, 1955; Hyde, 1960; Pfuetez, Watson & Pyle, 1960; Worobec, Krasner & Fox, 1960).

Thomas (1965) reported 1.7% of relapses in a 5-year follow-up of 483 sputum-positive patients (72 more could not be followed up), notified in Birmingham, England, who had been treated daily for about two years, first with the three main anti-tuberculosis drugs and subsequently, when pre-treatment sensitivity test results became available, by an appropriate 2-drug regimen; all the patients were in hospital for an "adequate" period of time and completed a period of therapy "to the satisfaction of the physician". Horne (1964; personal communication, 1965) from Edinburgh reported a

relapse rate of 2.8%, over an average follow-up of about six years (range 3-9 years), in 761 sputum-positive patients who had been successfully treated with triple-drug chemotherapy followed by a 2-drug regimen. (Over 10% of these patients had surgical treatment.) He found that the relapse rates were influenced by the duration of treatment; thus seven of 10 patients who had received less than six months' chemotherapy had a relapse, as compared with 13 of 171 who had received treatment for 6-18 months and one of 580 who had more than 18 months of treatment. Although the relapse rate of 8.7% for the 4-year follow-up in the present study is higher than those reported above, it cannot be regarded as unduly high in view of the regimen used and the duration of chemotherapy. Furthermore, if the patients with no residual cavitation at one year had *all* received isoniazid in the second year, and those with residual cavitation had continued with isoniazid plus PAS (see Great Britain, Medical Research Council, 1962), then the relapse rate would, in all probability, have been substantially lower than that reported here. However, if for economic or administrative reasons (Fox, 1964) it is not feasible to administer chemotherapy for more than one year, it is likely that a routine re-examination at two years would detect the majority of relapses, if indeed the patients had not already presented themselves for re-examination because of a recurrence of symptoms.

There has been considerable uncertainty concerning the prognosis of patients with the "open-negative" syndrome, but there is increasing evidence that this is not in itself a particularly dangerous state (Ryder, 1958; Worobec, 1959; Hyde, 1961). Our findings lend support to this view for, considering only those patients who received the placebo in the second year and thus had only one year of chemotherapy (isoniazid plus PAS), one (5%) of 19 with residual cavitation at one year had a relapse, as compared with seven (17%) of 42 without cavitation.

OCCURRENCE OF ISOLATED POSITIVE CULTURES

A positive culture occurring as an isolated event in any 6-month period, sometimes as late as the fifth year, was found in 18 (14%) of the patients with quiescent disease at one year, thus showing that, even in patients who did not have a bacteriological relapse, chemotherapy failed in some to be sterilizing. These isolated positive cultures usually showed only a very few colonies, were often isoniazid-sensitive and

were infrequently followed by a relapse (1 (6%) of 18 patients). This supports the observations of Raleigh (1957), Velu et al. (1960a, 1961a) and Devadatta et al. (1961) that an *isolated* positive result in patients with quiescent disease, who are under intensive bacteriological investigation, does not carry a bad prognosis.

OTHER ASSESSMENTS OF PROGRESS

This study has shown that measurements of ESR and assessments of changes in radiographic appearances and cavitation can often be misleading in following the progress of patients with bacteriologically quiescent disease. Thus, in patients with *persisting* quiescent disease over a 4-year period, radiographic changes, interpreted as deterioration, occurred at some time or other in 31%, increase in or appearance of cavitation occurred at five years in about 10%, and an elevated ESR was obtained for at least 60% of the patients at each of the yearly examinations.

THE RE-TREATMENT OF PATIENTS WITH ACTIVE OR RELAPSED DISEASE

Streptomycin plus pyrazinamide has been found to be an effective 2-drug regimen in the re-treatment of patients excreting isoniazid-resistant organisms, who had either failed to attain bacteriologically quiescent disease with the initial regimen of isoniazid plus PAS or who had a bacteriological relapse subsequently (Velu et al., 1960b, 1961b). Of the 34 patients in the present study who were treated with streptomycin plus pyrazinamide, one became unco-operative in the second month and refused further injections, one died of a non-tuberculous cause and two were still under treatment at five years. Of the remaining 30 patients, 17 (57%) achieved bacteriological quiescence of the disease.

Cycloserine plus ethionamide has also been found to be an effective 2-drug reserve regimen (Angel et al., 1963; Ramakrishnan et al., in preparation). In the present study, of five patients who received cycloserine plus ethionamide as a "third-line" regimen after failing to respond to streptomycin plus pyrazinamide, four had a favourable response while the fifth was still under treatment at five years. In contrast, cycloserine plus thioacetazone was disappointing, for all four patients who received it had an unfavourable response (see also Angel et al., 1963).

DISEASE STATUS AT FIVE YEARS OF ALL PATIENTS ORIGINALLY ADMITTED TO THE STUDY

It is of interest to consider the disease status at five years of all the patients admitted to treatment in the first year at home (96 patients) or in sanatorium (97 patients). Death due to a non-tuberculous cause occurred in five home and three sanatorium patients. Considering the remainder, 90% of the home patients and 89% of the sanatorium patients had bacteriologically quiescent disease at five years, 4% in each series had bacteriologically active disease and 5% and 6%, respectively, had died of pulmonary tuberculosis. It is noteworthy that only two patients, one in each series, had surgical treatment.

Considering all 193 patients admitted to the study, eight died of non-tuberculous causes and, of the remaining 185, 90% had bacteriologically quiescent disease at five years, 4% had active disease and 6% had died of tuberculosis. There was some evidence, albeit based on small numbers, that the outcome at five years was, relatively frequently, unfavourable in patients who had isoniazid-resistant organisms on admission to treatment, who discharged themselves prematurely from treatment or who had bacteriologically active disease at one year.

The results in the present series of patients do not compare unfavourably with other follow-up series reported from technically advanced countries (and covering approximately the same period of time, namely, 1956-62), especially in view of the very severe disease under treatment in the Madras series. Thomas (1965) reported a failure rate of 4.8% among 679 sputum-positive patients notified in Birmingham during the years 1957-58 and followed up for five years (77 more were untraceable and their failure rate is not known). Horne (1964; personal communication, 1965) had a failure rate of 1.8% in a hospital series of 771 sputum-positive patients followed up during 1955-60 in Edinburgh.

CONCLUSION

The 5-year findings abundantly confirm that the results of domiciliary chemotherapy, as carried out in this study, are sufficiently close to the results of sanatorium treatment to suggest that it is appropriate to treat the majority of patients at home (Tuberculosis Chemotherapy Centre, Madras, 1959; Velu et al., 1960a; Devadatta et al., 1961), despite the adverse environmental factors of poor diet

overcrowded living conditions and long hours of work often involving strenuous physical activity (Ramakrishnan et al., 1961b; 1966¹). It has also been shown that the family contacts of the patients who were treated at home were exposed to no special risk, either in the first year (Andrews et al., 1960) or over a 2-year period (Ramakrishnan et al.,

1961a) or over a 5-year period (Kamat et al., 1966²), in comparison with those of the patients treated in sanatorium in the first year. Considered together, these studies have firmly established the value of well-organized domiciliary chemotherapy, even in the most adverse environmental, economic and dietary circumstances.

IX. SUMMARY

1. A total of 193 patients was admitted to a controlled comparison of home and sanatorium treatment of pulmonary tuberculosis, all patients receiving a standard regimen of isoniazid plus PAS for one year. The present report deals with the progress of all these patients (96 home, 97 sanatorium) during the second, third, fourth and fifth years.

2. Of the 193 patients, 163 (82 home, 81 sanatorium), who had drug-sensitive organisms initially, were included in the main analysis and 30 were excluded because they did not conform to this or other important criteria.

3. Of the 163 patients in the main analysis, 130 had bacteriologically quiescent disease at one year, 10 had disease of bacteriologically doubtful status and 19 had active disease; four had died, three from tuberculosis and one from a non-tuberculous cause.

4. Of the 130 patients with bacteriologically quiescent disease at one year, 126 (57 home, 69 sanatorium) were randomly allocated to treatment during the second year, either with isoniazid alone or with a placebo, calcium gluconate; 65 (23 cavitated, 42 non-cavitated) received isoniazid and 61 (19 cavitated, 42 non-cavitated) the placebo.

5. During the 4-year period of follow-up, 11 (8.7%) of these 126 patients had a bacteriological relapse, eight of them in the first year of follow-up. Of the 57 home patients, four (7%) had a relapse, as compared with seven (10%) of 69 sanatorium patients. Of 84 patients with no residual cavitation at one year, seven (17%) of 42 who received calcium gluconate had a relapse, as compared with none of the 42 who received isoniazid ($P < 0.02$). Of the 42 patients with residual cavitation at one year, one (5%) of 19 who received calcium gluconate had a relapse, as compared with three (13%) of the 23 who received isoniazid. Six of eight patients in the

calcium series and one of three in the isoniazid series had a relapse with isoniazid-sensitive organisms.

6. Sixty patients, who received isoniazid alone in the second year and had bacteriologically quiescent disease at two years, were allocated at random to treatment in the third year, 30 to isoniazid alone and 30 to the placebo. There were no relapses in either group during the third, fourth or fifth years.

7. Of 18 (14%) patients who produced an isolated positive culture, only one had a bacteriological relapse subsequently.

8. Of the 10 patients with disease of bacteriologically doubtful status at one year, three had a bacteriological relapse; in all three, the positive culture at 12 months proved to be the commencement of a relapse. All 10 patients had bacteriologically quiescent disease at five years.

9. All of the 19 patients in the main analysis who had bacteriologically active disease at one year received further chemotherapy. At five years, 13 had bacteriologically quiescent disease, two had active disease and four had died, three from tuberculosis and one from a non-tuberculous cause.

10. Of the 30 patients excluded from the main analysis, those who had isoniazid-resistant organisms on admission and those who discharged themselves prematurely from treatment had, relatively frequently, an unfavourable outcome at five years.

11. Of the total of 193 patients admitted to the study, eight died from non-tuberculous causes during the 5-year period. Of the remaining 185, 90% had bacteriologically quiescent disease at five years, 4% had active disease and 6% had died of pulmonary tuberculosis. The proportion of patients who had quiescent disease at five years was very similar for the home and the sanatorium series, being 90% and 89%, respectively.

¹ See article on page 553 of this issue.

² See article on page 517 of this issue.

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RÉSUMÉ

Le Centre de Chimiothérapie de la Tuberculose à Madras, Inde, a suivi durant cinq ans l'évolution de la tuberculose pulmonaire chez 193 malades récents traités (97 au sanatorium et 96 à domicile) par l'association isoniazide-PAS pendant un an. Pour des raisons diverses, et notamment l'existence d'une résistance aux médicaments, 30 d'entre eux furent exclus de l'enquête principale, qui ne concerna dès lors que 163 cas pharmacosensibles, dont 82 traités à domicile et 81 au sanatorium.

Après cette année de traitement, la guérison bactériologique était obtenue chez 130 malades; chez 10 autres, elle ne pouvait être affirmée avec certitude; dans 19 cas, l'affection restait bactériologiquement active. Quatre décès furent observés, dont 3 dus à la tuberculose et 1 à une autre cause. Parmi les 130 patients ainsi négatifs après un an de traitement, 126 (57 à domicile, 69 au sanatorium) reçurent au cours de la 2^e année soit de l'isoniazide seul (65 sujets, dont 23 atteints de lésions cavitaires) soit du placebo, sous forme de gluconate de calcium (61 sujets, dont 19 atteints de lésions cavitaires).

Durant la période d'observation de quatre ans succédant à la 1^{re} année de traitement, 11 rechutes bactériologiques, soit 8,7%, furent notées chez ces 126 malades, dont 8 au cours de la 1^{re} année d'observation. Pour les 57 malades soignés à domicile, le taux des rechutes fut de 7% (4 cas), pour les hospitalisés, de 10% (7 cas). Sur les 84 patients sans lésions cavitaires résiduelles à l'issue de la 1^{re} année de traitement, 7 (17%) des 42 cas traités par placebo présentèrent une rechute; on n'en observa aucune chez ceux qui reçurent de l'isoniazide. Sur les 42 malades présentant des cavités résiduelles après la 1^{re} année de traitement, 5% (1 cas) des 19 sujets qui reçurent du placebo et 13% (3 cas) des 23 sujets qui reçurent de l'isoniazide furent victimes de rechutes. Dans 6 cas sur 8 après administration de placebo, et dans 1 cas sur 3 après traitement par l'isoniazide, les bacilles isolés lors des rechutes étaient sensibles à l'isoniazide.

Soixante malades traités par l'isoniazide seul durant la 2^e année et négatifs après cette période reçurent au cours de la 3^e année soit de l'isoniazide (30 cas), soit du placebo (30 cas). On ne nota aucune rechute dans ces deux groupes pendant les 3^e, 4^e et 5^e années de surveillance. Sur 18 malades (14%) ayant présenté une culture positive à une seule occasion, 1 seul eut une rechute par la suite.

Trois rechutes survinrent chez 10 malades bactériologiquement « douteux » à l'issue de la 1^{re} année de traitement, la positivité de la culture, dans ces 3 cas, ayant signé le début de la rechute. Ces 10 malades, après les cinq années d'observation, donnaient des cultures négatives.

Le traitement chimiothérapique fut poursuivi chez les 19 patients présentant une affection bactériologiquement active après la 1^{re} année de traitement. A l'expiration des cinq années de surveillance, 13 étaient négatifs, 2 donnaient encore des cultures positives et 4 étaient décédés, dont 3 de tuberculose et 1 d'affection non tuberculeuse.

Ceux des 30 malades exclus de l'enquête qui étaient porteurs de bacilles pharmaco-résistants ou qui abandonnèrent le traitement prématurément présentèrent de manière relativement fréquente un tableau clinique défavorable à la fin de la période d'observation de cinq ans.

Il y eut, parmi les 193 malades soumis à l'enquête, 8 décès dus à une cause non tuberculeuse. Sur les 185 sujets restants, on notait, après cinq ans, 90% de guérisons bactériologiques et 4% de tuberculoses pulmonaires évolutives, cependant que 6 décès par tuberculose pulmonaire avaient été enregistrés.

La proportion des guérisons bactériologiques à l'issue de la période d'observation était très voisine chez les personnes traitées à domicile ou au sanatorium (90% et 89% respectivement).

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